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Response to: Systematic review: animal studies of TB vaccines

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From Ann Williams[1], Sally Sharpe[1], Frank Verreck[2], Martin Vordermeier[3] and Glyn Hewinson[3]

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We write in response to the article by Kashangura *et al.*,[1] published on 8 September 2015, entitled 'Effects of MVA85A vaccine on tuberculosis challenge in animals: systematic review', in which the published efficacy data generated in our respective animal models on the TB candidate vaccine, MVA85A, were reviewed. This review is factually incorrect and, consequently, is potentially harmful to the process of vaccine development in a field where an effective vaccine is so urgently needed and where knowledge gaps hamper the swift and rationalized implementation of an improved vaccine strategy.

- An overarching theme of the review is that the animal studies were of poor quality. All institutes involved in the studies are in compliance with national laws and international directives; all studies were subject to independent ethical review before starting and, on submission for publication, were evaluated for ethical rigour by reviewers and editorial boards of independent journals. The review states that there was no randomization, baseline comparability was not described and blinding was not reported—these are standard requirements for obtaining ethical permission and the authors cannot justify claims that they were lacking from the experiments purely on the basis that it was not reported in the original publication.
- The language used in the review reflects emotive rather than scientific writing. To refer to animal 'death' is entirely incorrect and unwarranted, as humane endpoint criteria and euthanasia of animals were in place. The same applies to the term 'severe morbidity'. This misuse of terminology reflects a poor knowledge of animal experimentation and, in particular, of TB animal models. As far as the bovine infection model is concerned, it is designed as a preclinical, asymptomatic infection model that does not lead to clinical signs of bovine TB. This is reflected in the strictly defined endpoints, which in practice have never been reached. Thus the model is classified in the UK licensing scheme at the lowest level. It is unjustified and entirely incorrect, therefore, for the review by Kashangura *et al.*[1] to give the impression that animal suffering had occurred.
- The authors persistently refer to animal trials, but many of the studies were exploratory by nature and not efficacy trials of vaccine candidates. In particular, the non-human primate (NHP) and the cattle study designs were the first of their kind and were conducted in order to generate data which could be used to determine variability in effect size and to perform power calculations for subsequent studies.The guinea pig studies were conducted more than a decade ago and, as concluded by Williams *et al.*,[2] progression to humane endpoint as a primary measure of efficacy was subsequently shown not to be useful to discriminate small differences between test groups, particularly to demonstrate efficacy better than BCG. Accordingly, head-to-head testing of vaccines in the guinea pig model now employs an early, fixed endpoint of bacterial load in organs, which has high statistical and discriminative power.
- The authors have selected and extracted lung pathology or bacterial load data to perform their own analyses. There are several reasons why it is inappropriate to do this which include (but are not limited to) important differences in disease progression between the animal species, the dose, species and strain of *Mycobacterium* used and the time post-challenge that the measurements were made. The authors have completely overlooked the fact that several of these studies were designed to understand the impact of vaccines on the complex disease profile and were not a simple colony-forming unit (CFU) comparison between different treatment groups.
- All but one of the papers were published before the MVA85A clinical trial started, a fact which does not support the authors' final conclusion in the Abstract: 'We believe the results of the studies should be publicly available before embarking on trials in humans,

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irrespective of the findings'. We also support such an open approach, and this is exemplified by the large number of publications (many of which are listed in, and the subject of the review) where we report our findings on MVA85A, and several other vaccine candidates which have progressed to clinical trials. Despite it being explicitly highlighted in the original publication, Kashangura *et al.*[1] have failed to understand that the study which they consider to have been delayed was explorative and designed to assess a new infection strategy by using the aerosol challenge route. Such a study does not end when the *in vivo* phase is finished. The work was published after careful analysis of all parameters without any delay whatsoever.The statement that the results were published ' ... 2 years after this trial in monkeys had been completed' is curious since no dates were specified in the Sharpe *et al.*[3] publication which could allow this (erroneous) conclusion of deliberate delay to be made. Further, the cattle study referred to in this review was not conducted as a preclinical study for human TB vaccination but was aimed at the development of a cattle vaccine against bovine TB and the focus of the paper was on biomarker discovery. Any suggestion that this study was conducted as a preclinical study to support any human field trial is therefore without foundation.

In conclusion, our experiments have not only been misinterpreted but also portrayed as an isolated programme of work focused on the development of a single candidate. This is a gross misrepresentation of our efforts and the goals of the entire human TB vaccine field, which were (and still are) to pursue multiple vaccine candidates from preclinical models through to clinical efficacy trials, with the aim to identify an effective vaccine for humans and to subsequently define the predictive validity of the animal models.

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Authors' Response to: Letters re MVA85A

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We thank the authors of the letters for their interest in our systematic review of MVA85A vaccine on TB challenge in animals.[1]

Professor Helen McShane and colleagues point out that all trial-related decisions, including those made by ethics committees and regulators, were taken after consideration of all existing data from humans and animals, whether published or unpublished.[2] This is of course appropriate. It might be argued, with the benefit of hindsight, that greater emphasis might have been given, in the considerations by all of these parties, to signals in the animal data relating to progression of pathology and euthanasia endpoints, as summarized in our review. We believe that an important learning point from this experience is that independently conducted systematic review and meta-analysis of relevant animal data play an important role in such scientific, regulatory and ethical decisions for clinical trials in the future.

Dr Ann Williams and colleagues make a number of comments.[3] To reiterate, our purpose was: to summarize the reported study quality; to summarize results across the various outcomes reported; and to provide some insight into why the human trial was not successful. We did this using standard synthesis approaches in animal challenge studies. Dr Williams and colleagues challenge our

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